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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,752	VOORBERG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05/07/01, 10/29/02, 11/25/02, 09/10/03*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-86* is/are pending in the application.

4a) Of the above claim(s) *19,21-59,80 and 82-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,20,60-79,81,85 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 17-86 are pending.

2. Applicant's election without traverse of Group I, claims 17-18, 20, 60-81 and 85-86 (now claims 17-18, 20, 60-79, 81 and 85-86) drawn to a polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors, which polypeptide comprises the variable part of the heavy chain of a human antibody with factor VIII specificity or part thereof which at least includes the CDR3 region and a pharmaceutical composition thereof and DP-10 as the species filed on 10/09/03, is acknowledged.

3. A clear and obvious typographical error occurred in the restriction wherein claim 80 which reads on a polypeptide that specifically binds an antibody specific for factor VIII (an idotype antibody), was improperly included in Group I which are drawn to a polypeptide capable of specific binding to factor VIII. Therefore claim 80 belongs to non-elected Group II. Thus, claim 80 is drawn to nonelected inventions.

4. Claims 19, 21-59, 80 and 82-84 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

5. Claims 17-18, 20, 60-79, 81 and 85-86 are under examination as they read on a polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors, which polypeptide comprises the variable part of the heavy chain of a human antibody with factor VIII specificity or part thereof which at least includes the CDR3 region and a pharmaceutical composition thereof and DP-10 as the species.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 61-62, 65, 74-75 and 85-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The "polynucleotide" recited in claim 61, has no antecedent basis in base claim 60. Base claim 60 only recites a polypeptide.

2. Claim 62 is indefinite for reciting "at least about 4 amino acids". It is unclear how many amino acids constitute "about". One of skill in the art would not know if applicant meant 4 amino acid, as many as 6 amino acids, or even more.

3. Claim 65 is indefinite for being in improper format. The word "and" should be replaced with "or" before the last member of the species DP-77.

4. Claims 74-75 are indefinite in the recitation of "scFv-EL14" and "scFV-IT2", respectively, because their characteristics are not known. The use of "scFv-EL14" and "scFV-IT2" antibody as the sole means of identifying the claimed antibody renders the claim indefinite because "scFv-EL14" and "scFV-IT2" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct cell lines.

5. Claim 85 is rejected as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to obtaining the polynucleotide encoding polypeptide antibody specific for factor VIII.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 60-79 and 81 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

A. The phrase "an amino acid sequence from a complementarity-determining region of human antibody specific for factor VIII; an amino acid sequence that mimicks the factor VIII-binding of a complementarity-determining region of a human antibody specific for factor VIII; or a derivative of an amino acid sequence from a complementarity-determining region of a human antibody specific for factor VIII" claimed in claims 60(i-iii),

B. The phrase "comprises an amino acid sequence of at least about four contiguous amino acids from within an immunoglobulin heavy chain sequence or an immunoglobulin light chain sequence" claimed in claim 62, lines 2-3,

C. The phrase "the amino acid sequence of at least about four contiguous amino acids from within the immunoglobulin heavy chain sequence or the immunoglobulin light chain sequence comprise a sequence of at least four contiguous amino acids from a variable region" claimed in claim 63, lines 1-4,

represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 10/29/03 points to claims 9-13 and the specification at page 5, lines 14-26 for support for the newly added limitations as mentioned above in 9(A-C) as claimed in claims 60(i-iii), 80(i-iii), 62 and 63. However, the specification does not provide a clear support for such limitations. It is noted that original claims 9-12 recite a polypeptide comprising a *contiguous* amino acid sequence corresponding to or mimicking a *fragment* or *derivative* of a human antibody, wherein said fragment is (part of) a variable region of the heavy chain or light chain of said antibody and wherein said derivative is a single chain Fv fragment of said antibody. The original claims recite any binding fragment, but not limited to a CDR or four contiguous amino acids. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

10. Claims 17-18, 20, 60-79, 81 and 85-86 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Since the recombinant scFv fragments require both VL and VH domains and the specification does not provide SEQ ID NO for both scFv-EL14 and scFv-IT2 recited in claims 74-75. It is noted that the specification only provides VHEL-14 (SEQ ID NO: 23) and VHIT-2 (SEQ ID NO: 25). Therefore, the recombinant cells that produce the scFv-EL14 and scFv-IT2 antibodies are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

If the deposits have been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma has been deposited under the Budapest Treaty and that the hybridoma will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample *or for the enforceable life of the patent whichever is longer*. See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposits were made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the hybridoma described in the specification as filed are the same as that deposited in the depository.

Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Further, amendment of the specification to disclose the date of deposit and the complete name and address of the depository (ATCC.10801 University Boulevard, Manassas, VA 20110-2209) is required as set forth in 37 C.F.R. 1.809(d).

Furthermore, the specification does not reasonably provide enablement for any polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors, which polypeptide comprises the "variable part of the heavy chain" of a human antibody with factor VIII specificity or any "part thereof" which at least includes the CDR3 in claim 17, A polypeptide which essentially consists of (a) the CDR3 region of the variable part of the heavy chain of a human antibody with factor VIII specificity, (b) an antibody fragment containing the variable part of the heavy chain of a human antibody with factor VIII specificity, or a single Fv fragment containing the variable part of the heavy chain of a human antibody with factor VIII specificity in claim 18, or a pharmaceutical composition thereof in claim 20; any polypeptide comprising an amino acid sequence that "mimicks" the factor VIII-binding of a CDR of a human antibody specific for factor VIII or any "derivative" of an amino acid sequence from a CDR of a human antibody specific for factor VIII in claims 60 and 81, wherein said CDR is a CDR3 in claim 61, wherein the amino acid sequence of the polypeptide comprises an amino acid sequence of at least about four contiguous amino acids from within an immunoglobulin heavy chain sequence or an immunoglobulin light chain sequence in claim 62, wherein the amino acid sequence of at least about four contiguous amino acids from within the immunoglobulin heavy chain sequence or the immunoglobulin light chain sequence comprise a sequence of at least four contiguous amino acids from a variable region in claim 63. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. Besides the antibodies derivatives of svFv-EL-14 (DP-10), VHEL-14 (SEQ ID NO: 23), scFv-IT-2 (DP-14), CHIT2 (SEQ ID NO: 25), VH-IT2 (SEQ ID NO: 25, VH EL-5 (DP-14) (SEQ ID NO: 27) and VH EL-25 (DP-14) SEQ ID NO: 28 that bind C2-domain of factor VIII light chain, B38 (SEQ ID NO: 32), B18 (SEQ ID NO: 34), B35 (SEQ ID NO: 36), B04 (SEQ ID NO: 38) that bind A3-C1 domain of factor VIII light chain, the specification fails to provide guidance as to how to determine amino acids that mimicks the factor VIII-binding of a CDR or any derivative of an amino acid sequence from a CDR of a human antibody. Further the specification fails to provide guidance on which contiguous amino acids from within an Ig heavy chain or light chain sequence would provide the antibody specificity to factor VIII, the specification fails to provide such fragments.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a polypeptide having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that the polypeptides encompassed by the claims which may contain less than the full complement of CDRs from the heavy and/or light chain variable regions of a factor VIII antibody in unspecified order and derived from different germ lines framework sequence, have the required binding function. The specification provides no direction or guidance regarding how to produce such polypeptides as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional polypeptide antibody can be obtained by replacing the CDR regions of an acceptor antibody with the CDRs of a donor antibody such as CDR3. As evidenced by Adair et al. (US Patent 6,632,927) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (col.2 lines 58-61). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. Further, Panka et al teaches that the structural change responsible for the binding differences is due to a single amino acid substitution in the H chain framework region at position 94, at the edge of the CDR3. Panka et al teach that the finding that a framework mutation can alter binding to antigen is not unexpected (see Discussion). The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

Despite knowledge in the art for producing monoclonal antibodies to specific sequences, the specification fails to provide guidance regarding which "at least four amino acids" result in derivatives or mimicks that retain a similar function. Furthermore, while recombinant techniques are available, it is not routine in the art to screen large numbers of variants where the expectation of retaining similar function is unpredictable based on the instant disclosure.

Further, a fragment of the heavy chain can be any one of the constant regions (CH1-3) and also may be the hinge region. However, the language also reads on small amino acid sequences

which are incomplete regions of the constant region of the antibody. There is no support in the specification for linking the variable region to any or all of the myriad "fragments" which are encompassed within claim language. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed.

Also, at issue is whether or not the claimed composition of claims 20 and 81 would function as pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, and lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention.

11. Claims 17-18, 20, 60-79, 81 and 85-86 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an antibody that specifically binds factor VIII, antibodies derivatives of svFv-EL-14 (DP-10), VHEL-14 (SEQ ID NO: 23), scFv-IT-2 (DP-14), CHIT2 (SEQ ID NO: 25), VH-IT2 (SEQ ID NO: 25, VH EL-5 (DP-14) (SEQ ID NO: 27) and VH EL-25 (DP-14) SEQ ID NO: 28 that bind C2-domain of factor VIII light chain, B38 (SEQ ID NO: 32), B18 (SEQ ID NO: 34), B35 (SEQ ID NO: 36), B04 (SEQ ID NO: 38) that bind A3-C1 domain of factor VIII light chain for the diagnostic assay.

Applicant is not in possession of any polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors, which polypeptide comprises the "variable part of the heavy chain" of a human antibody with factor VIII specificity or any "part thereof" which at least includes the CDR3 in claim 17, A polypeptide which essentially consists of (a) the CDR3 region of the variable part of the heavy chain of a human antibody with factor VIII specificity, (b) an antibody fragment containing the variable part of the heavy chain of a human antibody with factor VIII specificity, or a single Fv fragment containing the variable part of the heavy chain of a human antibody with factor VIII specificity in claim 18, or a pharmaceutical composition thereof in claim 20; any polypeptide comprising an amino acid sequence that "mimicks" the factor VIII-binding of a CDR of a human antibody specific for factor VIII or any "derivative" of an amino acid sequence from a CDR of a human antibody specific for factor VIII in claims 60 and 81, wherein said CDR is a CDR3 in claim 61, wherein the amino acid sequence

of the polypeptide comprises an amino acid sequence of at least about four contiguous amino acids from within an immunoglobulin heavy chain sequence or an immunoglobulin light chain sequence in claim 62, wherein the amino acid sequence of at least about four contiguous amino acids from within the immunoglobulin heavy chain sequence or the immunoglobulin light chain sequence comprise a sequence of at least four contiguous amino acids from a variable region in claim 63.

Applicant has disclosed only antibody that specifically binds factor VIII, antibodies derivatives of svFv-EL-14 (DP-10), VHEL-14 (SEQ ID NO: 23), scFv-IT-2 (DP-14), CHIT2 (SEQ ID NO: 25), VH-IT2 (SEQ ID NO: 25, VH EL-5 (DP-14) (SEQ ID NO: 27) and VH EL-25 (DP-14) SEQ ID NO: 28 that bind C2-domain of factor VIII light chain, B38 (SEQ ID NO: 32), B18 (SEQ ID NO: 34), B35 (SEQ ID NO: 36), B04 (SEQ ID NO: 38) that bind A3-C1 domain of factor VIII light chain; therefore, the skilled artisan cannot envision all the contemplated polypeptide sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 60-66, 70-73, 76-79 and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Lenting et al (J Biol. Chem, 269:7150-7165, 1994).

Lenting et al teach antibody mimicks and derivative of a human antibody specific for factor VIII such as CLB-CAg A, CLB-CAg 12, CLB-CAg 69, and CLB-CAg 117 against FVIII-LC and CLB-CAg 9 against FVIII-HC (see page 7150, under Antibodies, in particular). Lenting et al further teaches the antibodies in a buffer containing 0.15 M NaCl, 1% (W/v) HAS, 25 mM Tris (pH7.2) (see page 7151 under FVIII binding properties of monoclonal antibodies, in particular). Lenting et al teach that CLB-CAg A is known to be a strong inhibitor of FVIII activity and has its epitope within the A3 domain sequence Gln^{1778}-Asp^{1840} of the FVIII-LC (see page 7151, last paragraph in particular). Finally, Lenting et al teach that antibody CLB-CAg A effectively inhibited FIXa binding to the FVIII-LC (see fig 6, page 7154, in particular).

Claim 81 is included because Lenting *et al* teach the CLB-CAg A antibody to human VIII-LC in a buffer solution which is also consider to be a pharmaceutically acceptable carrier.

While the prior art teachings may be silent as to the "which at least includes the CDR3 region" in claim 17, "the CD3 region of the variable part of the heavy chain of a human antibody" claimed in claim 18, "comprises an amino acid sequence from a complementarity-determining region" in claim 60, "wherein said complementarity-determining region is a CDR3 region" in claim 61, "wherein the amino acid sequence of the polypeptide comprises an amino acid sequence of at least about four contiguous amino acids from within an immunoglobulin heavy chain sequence of an immunoglobulin light chain sequence" in claim 62, "wherein the amino acid sequence of at least about four contiguous amino acids from within the immunoglobulin heavy chain sequence or the immunoglobulin light chain sequence comprise a sequence of at least four contiguous amino acids from a variable region" in claim 63, "wherein the variable region is a heavy chain variable region" in claim 64, "wherein the heavy chain variable region is derived from one of the following:DP-10, DP-14, DP-15, DP-31, DP-47, DP-49 or DP-77" in claim 65, "wherein the polypeptide reduces the activity of factor VIII inhibitors of haemophilia A patients" in claim 76, "wherein the factor VIII inhibitors of haemophilia A patients are antibodies spepcific for factor VIII" in claim 77' per se; the referenced antibody mimicks and derivative are the same as the claimed antibody mimicks and derivative. Therefore limitations are considered inherent properties of the referenced antibody.

The reference teachings anticipate the claimed invention.

14. Claims 17-18, 20, 60-68, 71, 73, 76-79 and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Fijnvandraat et al (Blood, 91:2347-2352, April 1998) (IDS Ref. No. 9).

Fijnvandraat et al teach inhibitory antibodies derived from hemophilia A patient's plasma directed against factor VIII. The human alloantibody interferes with binding of factor IXa to factor VIII light chain (see abstract, page 2347, in particular). Fijnvandraat et al further teach that binding of the majority of antibodies to in vitro synthesized factor VIII fragments was dependent

on the presence of amino acid residues Gln^{1778}-Met^{1823} (A3 domain), a region known to contain a factor IXa binding site. Furthermore, Fijnvandraat et al teach that the purified IgG antibodies inhibited binding of factor IXa to immobilized factor VIII light chain in a dose-dependent manner (see abstract in particular). Fijnvandraat et al show that the predominantly IgG4 antibodies accounted for binding to the labeled factor VIII-LC (see page 2349, 1st col., lines 3-4, in particular). Finally, Fijnvandraat et al teach the purified IgG from patient's serum were incubated in a buffer containing 20 mMol/L Histidine, 100 mM NaCl, 5 mM CaCl2 and 0.1% Tween-20 (see page 2348, 2nd col., under binding assays in particular).

Claims 20 and 81 is included because Fijnvandraat et al teach the IgG antibodies a buffer solution which is also consider to be a pharmaceutically acceptable carrier.

Claim 65 is included because the inhibitory antibodies derived from hemophilia A patent's plasma inherently would be derived from those germ lines.

While the prior art teachings may be silent as to the "which at least includes the CDR3 region" in claim 17, "the CD3 region of the variable part of the heavy chain of a human antibody" claimed in claim 18, "comprises an amino acid sequence from a complementarity-determining region" in claim 60, "wherein said complementarity-determining region is a CDR3 region" in claim 61, "wherein the amino acid sequence of the polypeptide comprises an amino acid sequence of at least about four contiguous amino acids from within an immunoglobulin heavy chain sequence of an immunoglobulin light chain sequence" in claim 62, "wherein the amino acid sequence of at least about four contiguous amino acids from within the immunoglobulin heavy chain sequence or the immunoglobulin light chain sequence comprise a sequence of at least four contiguous amino acids from a variable region" in claim 63, "wherein the variable region is a heavy chain variable region" in claim 64, "wherein the heavy chain variable region is derived from one of the following:DP-10, DP-14, DP-15, DP-31, DP-47, DP-49 or DP-77" in claim 65, "wherein the polypeptide reduces the activity of factor VIII inhibitors of haemophilia A patients" in claim 76, per se; the referenced antibody mimicks and derivative are the same as the claimed antibody mimicks and derivative. Therefore limitations are considered inherent properties of the referenced antibody.

The reference teachings anticipate the claimed invention.

15. Claims 17-18, 20, 60-68, 71, 73, 76-79 and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Scandella (International Journal of Pediatric Hematology/Oncology, 1:437-447, 1994).

Scandella teaches human alloantibodies and autoantibodies which inactivate Factor VIII and derived from hemophilia A patient's plasma (see page 438, Immunoblotting Assay, and Tables I and II in particular). Scandella further teaches that there was a predominance of IgG4 in both types of antibodies (page 443 under IgG subclass, in particular) Scandella teaches that the epitope specificity of alloantibodies and autoantibodies inhibitor appeared to be similar and that the epitopes are A2, A2+A-1-A2, C2, A2+C2 or A2+C2+A3 (Table I) and A2, C2, A2+C2

(Table II) (see table I and II in particular). Furthermore, scandella shows that anti-fVII antibodies are functional inhibitors using neutralization assays and recombinant fragments of fVIII (see page 444, 2nd col., 2nd paragraph in particular). Scandella teaches that the epitope mapping and functional neutralization of both alloantibody and autoantibody inhibitors indicts that these anti-fVIII antibodies which arise under very different circumstances cannot be distinguished so far on the basis of these characteristics (see page 444, 2nd col., 4th paragraph in particular). Finally, Scandella teaches that either the anti-A2 or the anti-C2 antibodies in a plasma containing both of them may be the predominant inhibitor (see abstract in particular).

Claims 20 and 81 is included because Scandella teaches the antibodies in plasma which is also consider to be a pharmaceutically acceptable carrier.

Claim 65 is included because the inhibitory antibodies derived from hemophilia A patent's plasma inherently would be derived from those germ lines.

While the prior art teachings may be silent as to the "which at least includes the CDR3 region" in claim 17, "the CD3 region of the variable part of the heavy chain of a human antibody" claimed in claim 18, "comprises an amino acid sequence from a complementarity-determining region" in claim 60, "wherein said complementarity-determining region is a CDR3 region" in claim 61, "wherein the amino acid sequence of the polypeptide comprises an amino acid sequence of at least about four contiguous amino acids from within an immunoglobulin heavy chain sequence of an immunoglobulin light chain sequence" in claim 62, "wherein the amino acid sequence of at least about four contiguous amino acids from within the immunoglobulin heavy chain sequence or the immunoglobulin light chain sequence comprise a sequence of at least four contiguous amino acids from a variable region" in claim 63, "wherein the variable region is a heavy chain variable region" in claim 64, "wherein the heavy chain variable region is derived from one of the following:DP-10, DP-14, DP-15, DP-31, DP-47, DP-49 or DP-77" in claim 65, "wherein the polypeptide reduces the activity of factor VIII inhibitors of haemophilia A patients" in claim 76, per se; the referenced antibody mimicks and derivative are the same as the claimed antibody mimicks and derivative. Therefore limitations are considered inherent properties of the referenced antibody.

The reference teachings anticipate the claimed invention.

16. Claims 17-18, 60-64, 66, 69,70-73, 76-79 are rejected under 35 U.S.C. 102(b) as being anticipated by Davies (Davies et al 1997, thromb. Haemostas. Supplement: 2352).

Davies et al teach eight human FVIII specific scFvs were selected by panning on immobilized rFVIII. Further, Davies et al teach obtaining the immunoglobulin V(ariable) domain structure of immune FVIII antibodies obtained by V gene phage display technology from 3 Haemophilia A patients with peak inhibitor levels about 60Bu/ml. Davies et al teaches that 3 patients have antibodies against the A2 domain and 2 patients have antibodies to the light chain. Davies et al

teach the method of producing a recombinant scFvs specific for Factor VIII by obtaining the primary structure of the variable domains of factor VIII antibodies obtained from inhibitor patient B cells RNA by V gene phage display technology. The VH gene cDNA was obtained by reverse transcription of lymphocytic RNA from the 3 patients with an IgG specific primer and amplified by the PCR with appropriate VH and joining gene primers. The amplified VH gene repertoire was cloned for display as single chain V domain fragments (scFv) on the surface of the phagemid vector PhEN-2-VL. Each library contained 10^7 individual clones (see the abstract in particular).

While the prior art teachings may be silent as to the "which at least includes the CDR3 region" in claim 17, "the CD3 region of the variable part of the heavy chain of a human antibody" claimed in claim 18, "comprises an amino acid sequence from a complementarity-determining region" in claim 60, "wherein said complementarity-determining region is a CDR3 region" in claim 61, "wherein the amino acid sequence of the polypeptide comprises an amino acid sequence of at least about four contiguous amino acids from within an immunoglobulin heavy chain sequence of an immunoglobulin light chain sequence" in claim 62, "wherein the amino acid sequence of at least about four contiguous amino acids from within the immunoglobulin heavy chain sequence or the immunoglobulin light chain sequence comprise a sequence of at least four contiguous amino acids from a variable region" in claim 63, "wherein the variable region is a heavy chain variable region" in claim 64, "wherein the polypeptide reduces the activity of factor VIII inhibitors of haemophilia A patients" in claim 76, per se; the referenced antibody mimicks and derivative are the same as the claimed antibody mimicks and derivative. Therefore limitations are considered inherent properties of the referenced antibody.

The reference teachings anticipate the claimed invention.

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 85-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fijnvandraat et al (Blood, 91:2347-2352, April 1998) (IDS Ref. No. 9) or Scandella (International Journal of Pediatric Hematology/Oncology, 1:437-447, 1994) or Davies et al in view of Marks et al (J. Mol. Biol. 222:581-597, 1991) IDS Ref. No. 12.

The teachings of by Fijnvandraat *et al,* Davies *et al* and scandella have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a method for producing and isolating a polypeptide antibody in claims 85-86.

Marks et al teach a method of producing a recombinant polypeptide antibody (human antibodies), antibody fragment or derivative such as scFv fragments comprising providing a recombinant vector in a suitable host cell; the vector comprising a polynucleotide encoding said polypeptide operably linked to a control sequence for expression of the polynucleotide from the vector in the host cell, and expression the polypeptide in the host cell and then isolating the polypeptide (see abstract, Fig 1, page 586, under Purification of scFC and affinity determination, in particular). Marks et al teach that a single large phage display library can be used to isolate human antibodies against any antigen, by passing both hybridoma technology and immunization (see abstract in particular). Marks et al concluded that human antibodies of many specificities can be made in the future by panning a single large natural phage display library with antigen (see page 595, last paragraph in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the polypeptide antibody taught by Fijnvandraat et al, scandella, or Davies et al using the method, host cells and the method of isolation as taught by Marks *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such a method provides a single large phage display library that can be used to isolate human antibodies against any antigen, by passing both hybridoma technology and immunization as taught by Marks *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claim 69 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fijnvandraat *et al* or Schandell in view of Bird *et al* (1988).

The teachings of Fijnvandraat *et al* and scandella references, have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a single chain antibody in claim 69.

Bird *et al* teach a single chain antigen binding proteins composed of an antibody variable light – chain amino acid sequence (V_L) tethered to a variable heavy –chain sequence (V_H) by a designed peptide that links the carboxyle terminus of the V_L sequence to the amino terminus of the V_H sequence. Bird *et al* further teach that the single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion (see the entire document and page 426, left column, 2nd paragraph in particlular)).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the antibody taught by either Fijnvandraat *et al* or Scandella as a single chain antibody as taught by the Bird *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion as taught by Bird *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. Claims 20 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davies et al in view of U.S Patent No. 4,731,245.

The teachings of Davies et al reference, have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a composition with a pharmaceutically acceptable carrier in claims 20 and 81.

The `245 patent teaches a composition comprises the antibody, as the active ingredient in association with a pharmaceutically acceptable carrier. Advantageously, the composition can be formulated in dosage unit form. The amount of the active ingredient contained in each dosage unit may be adjusted so as to enable the administration of the antibody at a daily dose (see col., 7 line 63 through col., 8 line 3 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the antibody fragments taught by Davies et al in a composition with a pharmaceutically acceptable carrier as taught by the `245 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the composition can be formulated in dosage unit form. Further, the amount of the

active ingredient contained in each dosage unit may be adjusted so as to enable the administration of the antibody at a daily dose as taught by the '245 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

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January 8, 2004

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